digestibility, color, and physical state] reduce the ability of the indoxyl compounds and the extra-cellular precipitate to move by at least one of diffusion and convective flow in the extracellular fluid.

80. (twice amended) A therapeutic agent in accordance with claim 69 in which each of the indoxyl compounds includes 5,5-bi-indoxyls attached at position 5 of the indoxyl compounds to [alter the solubility. digestibility, color, and physical state] reduce the ability of the indoxyl compounds and the extra-cellular precipitate to move by at least one of diffusion and convective flow in the extracellular fluid.

REMARKS

Reconsideration and allowance are respectfully requested.

Claims 69, 71, 72, 75, and 77-80 have been amended to provide a better definition of the invention. It is submitted that these amendments to the claims neither constitute new matter nor raise new issues and therefore should be entered.

RESPONSES TO THE SECTIONS OF THE OFFICIAL ACTIONS AND TELEPHONE INTERVIEWS WITH THE EXAMINER

The following are submissions, comments, and arguments in response to the numbered Sections of the Official Action, mailed November 25, 1998, the interview summaries of telephone interviews of the undersigned with the Examiner, and the Official Advisory Action, mailed August 16, 1999.

I. DECLARATIONS

Attached hereto are Declarations of Professor Emer. Henry Rapoport, Ph.D. and Professor Alan L. Epstein, M.D., Ph.D., each under 37 CFR § 1.132 traversing the grounds of rejection as identified by the Section numbers recited therein of the Official Action, mailed November 25, 1998.

II. SECTIONS OF THE OFFICIAL ACTION MAILED NOVEMBER 25, 1998

Action, Section 3, page 2

> "...a review of the specification revealed that there is not an adequate description of each drawing"

Response:

It is submitted that the Brief Description of the Drawings on pages 14-16 of the specification is in complete compliance with 37 § C.R.F.§ 1.74 and MPEP § 608.01(f):

1.74 Reference to drawings

> "When there are drawings, there shall be a brief description of the several views of the drawings and the detailed description of the invention shall refer to the different views by specifying the numbers of the figures and to the different parts by use of reference letters or numerals (preferably the latter)."

Furthermore, the detailed description of the invention beginning on page 17 of the specification completely conforms to the requirement of 37 C.F.R.§ 1.71 and MPEP § 608.01 in that each reference numeral and each drawing is specifically and completely identified and described in the specification.

Action, Section 5, pages 3-4, (a')

> '...a review of the cited support reveals general teachings of the chemistry of indoxyl chemistry but does not provide either guidance on or exemplification of making or using the broadly claimed agents, that would be therapeutic when administered *in vivo*. Further, the issue raised here is not only whether the making/using if soluble precipitable material is disclosed in the specification but also that the applicant has not taught how to make or use the instant invention, especially in view of Applicants (page 15, section 21 of Paper No. 14) admission on the record that the therapeutic agent is "only therapeutic after it has been converted into an insoluble material because the therapeutic effect depends on the radiation field which is generated by the precipitate induced immobilization the isotope and its long term retention at the immobilized site." A review of the specification

does not reveal the absolutely critical nature of radio-labeling of the therapeutic agent...'

Response:

1. Making Soluble Precipitable Material

See the Declaration of Professor Emer. Henry Rapoport, Ph.D.

Making indoxyls as the soluble precipitable material is found in specification pages 20-23. Making the soluble precipitable material comprised of soluble and insoluble moiety is found in specification pages 23-24. The method of radio-labeling the therapeutic agent is described in the specification (page 23) and in Figs. 15-17.

2. Using Soluble Precipitable Material

See the Declaration of Professor Alan L. Epstein, M.D., Ph.D.

The method and dosages of the bispecific reagent and the therapeutic agent in the present invention are readily taught by the prior art of ADEPT disclosed in the specification. In the present invention the therapeutic agent (the soluble precipitable material) and in the prior art of ADEPT, the prodrug, are both converted by the non-mammalian enzyme moiety of a previously bound bispecific reagent. In the present invention, the therapeutic agent which is a soluble precipitable material is enzymatically converted into an insoluble precipitate. In ADEPT, a soluble pro-drug is enzymatically converted into an active soluble drug.

It is widely known and published in the field that the immobilization of radio-isotopes can be used successfully for therapy. Examples have also been given in the specification of the invention on pages 7-8, and 11. The immobilization of isotopes generates radiation fields that kill cancer cells in the immediate microregion of the deposited isotopes.

In accordance with the invention the "first therapeutic agent" (being a soluble

precipitable material) is not therapeutic per se when administered *in vivo.* It only becomes therapeutic as disclosed in the specification when it is concentrated and retained in situ.

Action, Section 5, page 4, (b'), (c'), and (d')

> '...a review of pages 9 and 10 reveals the disclosure of numerous references which report the enzymatic conversion of a pro-drug to an active drug in the extracellular space, however, none of the cited references have been submitted and therefore none of the references have been considered. However, it is noted that on page 10, paragraph 2, the specification clearly states that "ADEPT approach fails to successfully treat cancer", thus dosage and methods of administration used in the prior art would not be expected to enable the instant claims, further, it is noted that the cited references are to be found in the "Prior Art" section of the specification and that neither guidance on nor exemplification of administration or exemplification of or guidance for effective dosage are to be found in the portion of the specification drawn to the invention (c' and d'). As disclosed above the teachings on page 20-24 are drawn to indoxyl chemistry and no teaching or exemplification is provided for any of the other therapeutic reagents claimed and the argument is not found persuasive for the reasons disclosed in section (b') above,...'.

Response:

See Declaration of Professor Alan L. Epstein, M.D., Ph.D.

Applicant has included a sample of the references for ADEPT cited in the specification of the application.

Although ADEPT fails to treat cancer successfully, the dose levels of the prodrug are relevant guidelines for dose levels for the therapeutic agent and the bispecific reagent in the present invention. ADEPT fails for reasons other than the administered dose of the prodrug--most importantly because the active drug (which is produced by the enzymatic action of the

enzyme moiety of the bispecific reagent converting a pro-drug into an active drug) diffuses away from its site of production to enter the blood stream where it exerts a systemic toxic effect. The larger the tumor, the larger will be the number of production sites, and the larger will be the number of active drug molecules which will diffuse into the blood to have a large systemic toxicity.

However, in the present invention, the attack against the cancer is determined by the number of radio-isotope atoms which are immobilized, which is determined by the number of enzyme molecules which are bound (via the bound bispecific reagent) and the turn-over number of the enzyme ("turn-over number" is the number of molecules that can be converted from one state to another per unit time per molecule of enzyme).

See also Applicant's response to Action, pages 3-4, (a') above.

Action, Section 5, page 4, (e')

> "...the argument is drawn to the bispecific reagent, however, as clearly repeated on page 8 of the response, the issue raised here is that the therapeutic agents may be inactivated *in vivo* and because the applicant did not distinctly and specifically point out the supposed errors rejection, the rejection is maintained,..."

Response:

The therapeutic agent is not a protein and proteolytic degradation is, therefore, not relevant. The therapeutic agent is a radio-labeled soluble precipitable material. It circulates freely in all body fluid which of course includes, as recited in official Action "fluids, cells and tissues". Since the therapeutic agent is only converted into an insoluble material by the non-mammalian enzyme moiety of the bound bispecific reagent, this is the only location where it will be immobilized and be retained for a long time, and therefore, this will be the only location where it will generate radiation fields (which destroy all cancer cells in the immediate microregion surrounding each location of the bound non-mammalian enzyme) and provide a therapeutic effect. The agent is only therapeutic after it has been converted into

an insoluble material because only when immobilized, does a sufficiently large number of radio-active isotopes become deposited and be retained for a sufficiently long time. In all other locations, it may exert a minor injury and toxicity (because it is radio-labeled), but the radiation dose is not sufficient to produce a therapeutic effect. Immunological inactivation is unlikely to be an issue because the administration of the therapeutic agent will be the first time the host has been exposed to the novel agent.

Action, Section 5, pages 4, 5, (f')

> '...although the word "adapted" has indeed been replaced in the recited claims, the argument drawn to dosage and methods of administration is not found persuasive for the reasons set forth in section (b') above,...'.

Response:

See Applicant's response to "Action, section 5, page 4, (b'),(c'), and (d')" above.

Action, Section 5, page 5, (g')

> "...as recited in claim 69, the term therapeutic agent includes peptides, carbohydrates, chitosan, chitin, proteoglycans and synthetic polymers as well as indoxyl compounds and contrary to applicant's arguments, peptides, which read on proteins, and protoglycans are claimed Claim 69 specifically claims that the therapeutic agent (as identified by the claim) is converted into a extracellular precipitate which the claim defines as an insoluble and non-digestible precipitate and further Applicant admits on the record that the specification does not describe proteins and peptides as candidates for the soluble precipitate material. (h') the argument is not persuasive for the reasons previously disclosed in the section (a') and (c') above,...".

Response:

The original claims are part of the disclosure of the application: In re Meyers (CCPA 1969) 410 F2d 420,161 USPQ 668, and the disclosure can be amended to conform with the former. Ex parte Wilson et al (POBA 1957) 116 USPQ 595. See MPEP in 608.1(1), 608.4.

706.03(o), 2163.06, 2163.06, "III"

In response to the allegation that the specification does not describe proteins and peptides, as candidates for the soluble precipitable material, applicant submits that original claim 5 recites:

> "... in which the first therapeutic agent is a soluble agent and is an organic chemical comprising at least one of peptides, including opio-melanins, of carbohydrates including cellulose, chitosan, and chitin, and of proteoglycans, of synthetic polymers, and of indoxyl compounds having molecular positions 1-7."

Action, Section 5, page 5, (h')

"...the argument is not persuasive for the reasons previously disclosed in section (sic) 5, (a') and (c') above.

Response:

See Applicant's response to "Action, Section 5, pages 3-4, (a')" above and to "Action, Section 5, page 4, (b'), (c'), and (d')" above.

Action, Section 5, page 5, (I')

> "...Applicant's stated opinion is noted but it is clear that one of skill in the art would expect that an insoluble precipitate would be removed from the claimed region either by convection, diffusion, or by phagocytosis. Applicant is invited to submit objective evidence demonstrating that the insoluble precipitate will not diffuse away, move away or be removed from the area by phagocytosis. As drawn to the tethering of the precipitate, applicant is arguing limitations not recited in the claims as presently constituted. It is noted that amendment of the claims to recite tethering limitations in an amendment submitted after final would raise a new issue not previously considered, and that the amendment would not be entered for this reason."

Response:

See Declaration of Professor Alan L. Epstein, M.D., Ph.D.

In the proposed invention, the product of the enzymatic conversion is insoluble and stable. Insoluble materials do not diffuse--only soluble materials diffuse. In the present invention, the insoluble precipitate is not removed from the area by convective flow because tumors lack effective lymphatic drainage (see references in specification pages 35-36). Further, in the present invention, the insoluble precipitate is not removed from the area by phagocytic activity because macrophage and phagocytic activity in the tumor is reduced (see references in specification pages 35-36).

For example, trypan blue adsorbed to albumin (a soluble macromolecule) is retained in tumor tissue for over 5 days, whereas it only remains in normal tissue for a few hours--this difference reflects the fact that normal tissues, but not cancer tissues, have an effective lymphatic drainage. Those skilled in the art would understand that this difference (hours in normal tissues and days in cancer tissue) would be amplified for insoluble materials. This is confirmed by the long term retention of insoluble DNA which has been relocated from inside cells to the extra-cellular fluid.

Ultimately, the insoluble precipitate will be removed by convection and phagocytosis. However, in accordance with the present invention, such removal from tumor tissue will be slower than from normal tissues. This difference is a "window of opportunity" for the therapist.

Action, Section 6, page 6, (a')

> "...because the issue raised here is not whether the instant invention circumvents problems related to impermeability of tumors to antibodies and lack of uniform distribution of antibodies, but rather whether the instant specification is enabling. For the reasons stated, one of skill in the art would be forced into undue experimentation to practice the claimed invention,...".

Response:

See Applicant's response to "Action, Section 5, page 4 (b'), (c'), and (d')" above.

Action, Section 6, page 6, (b')

"... for the reason previously disclosed in Section 5(b') above,..."

Response:

See Applicant's response to "Action, Section 6, page 6, (a')" above.

Action, Section 6, page 6, (c')

"...a review of the cited pages reveals support for the advantage of a therapeutic agent to be made cell impermeant (p. 19) but no discussion drawn to making soluble precipitable material into a cell impermeant molecule on page 22 and 29-30."

Response:

The specification in referring to making the soluble precipitable material cell impermeant on page 19 recites that "the first therapeutic agent can be made cell impermeant by attaching one of a number of cell impermeant molecules at least including peptides or polymers having a molecular size greater than 1,000 Daltons and anionic chemicals including thiols."

See also Applicant's response to "Action, Section 8, page 7" below.

Action, Section 8, page 7

"Applicant argues that making the soluble precipitable material into a cell impermeant molecule is described at pages 19, 22, and 29-30.
The argument has been noted but has not been found persuasive."

Response:

See Applicant's response to "Action, Section 8, page 7," below.

Action, Section 8, page 7

> "Applicant argues that making the soluble precipitable material into a cell impermeable molecule is disclosed on pages 19, 22 and 29-30. The recitation of materials having a molecular weight of greater than 1000 Daltons defines a large molecule and thereby a cell impermeant chemical. The argument has been noted, but has not been found persuasive for the reasons disclosed in 6(c') above. Further, the issue raised here was not the definition of a large molecule that is cell impermeant but rather the issue raised was how to use a large molecule, as broadly claimed, that will function as claimed."

Response:

See Declaration of Professor Emer. Henry Rapoport and Declaration of Professor Alan L. Epstein, M.D., Ph.D.

Action, Section 9, page 7

> "Applicant argues that, as drawn to the rejection 6(e) (Paper No. 10, Section 6, pages 11-16) that the therapeutic agent is radio-labeled. The argument has been noted but has not been found persuasive as drawn to claims 69-82, because radio labeling is only claimed in claim 83 which is dependent upon claim 69."

Response:

The first therapeutic agent is radio-active and, therefore, must cause some cell damage to cancer cells and all normal systemic cells while it is soluble and circulating in the body fluids. This cell damage does not prevent the first therapeutic agent being therapeutic because the concentration of the radio-active molecule in the body fluid is low and because it does not remain in the body fluids for a long time. When the soluble first therapeutic agent is converted into an insoluble material, the concentration of radio-active molecule in the precipitate is high and also because it is retained *in situ* for a very long time. The combined effect of high concentration and long term retention is to generate an intense radiation field that destroys cancer cells and is, thus, therapeutic after its conversion to the insoluble and

non-digestible precipitate.

Action, Section 9, page 7

> "Applicant argues that, as drawn to the rejection 6(f) (Paper No. 10, Section 6, pages 11-16) that as drawn to "disposed"the precipitate is formed by the catalytic action of the non-mammalian enzyme. The argument has been noted but has not been found persuasive because the term "disposed" has not been defined by either the claim or the specification."

Response:

Applicant has amended Claim 69 herein to provide a better definition of the invention.

Action, Section 9, page 7

> "Applicant argues that, as drawn to rejection 6(I) that the markush grouping is proper because the members of the group possess a property in common. The argument has been noted but is not persuasive because it is not clear whether the peptides and carbohydrates claimed are limited to those recited in the claim or whether they include other moieties of the same class."

Response:

Since a markush group by definition defines a constructed group of constituents, the Applicant is entitled to equivalence of said constructed group.

Action, Section 9, page 8

> "The argument has been noted but has not been found persuasive (sic) a review of the cited pages reveals support for the advantage of a therapeutic agent to be made cell impermeant (p.19) but no discussion drawn to making soluble precipitable material into a cell impermeant molecules on pages 22 and 29-30 and does not define the claimed materials and further the recitation of weight of greater than 1000 Daltons does not define the metes and bounds of the claimed invention."

Response:

The specifications referring to making the soluble precipitates material cell

improvement is found on page 19 (not pages 22, and 29-30).

See also Applicant's two responses to "Action, Section 8, page 7", above.

Action, Section 9, page 8

"The argument has been noted but has not been found persuasive because although the claim has been amended to recite the effects of altering indoxyl compounds, the claim has not been amended to define derivatives of benzyloxy compounds."

Response.

Claim 79 has been amended by the Applicant to provide a better definition of the invention.

Action, Section 10, page 9

"The argument has been noted but has not been found persuasive because of the broadly recited prodrugs in WO 91/09134. Applicant is invited to submit objective evidence to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product, particularly as drawn to the anti-cancer drugs recited on page 9, line 14 through page 11."

Response:

See Declaration of Professor Alan L. Epstein, M.D., Ph.D.

Action, Section 9 (sic), page 9

Objections to previously amended claim 69.

Response:

Claim 69 amended in view of "Action, Section 9, page 9" is submitted herein.

Action, Section 11, pages 9, 10

> "The limitation of "at least several days" in claim 69 and the limitation of "alter solubility, digestibility, color and physical state" in claims 78-80 have no clear support in the specification and the claims as originally filed."

Response :

Claim 69 and claims 78-80 have been amended herein to provide a better definition of the invention.

III. SECTIONS OF THE OFFICIAL ADVISORY ACTION MAILED AUGUST 16, 1999 PAPER No. 19

A. With the Amendment filed on May 25, 1999, there were submitted Declarations Under 37 CFR § 1.132 Traversing Grounds Of Rejection by each of Professor Alan Epstein, M.D., Ph.D., Professor in the Department of Pathology at the University of Southern California, dated May 24, 1999 and by Henry Rapoport, Emeritus Professor of Chemistry at the University of California, Berkeley, dated May 24, 1999.

In the Advisory Action, mailed August 16, 1999, the Examiner states on page 5 in Section 3:

> "Applicant argues that Declarations of Professor Rapoport and Dr. Epstein are drawn to the issue raised. The argument has been noted but has not been found persuasive because the Declarations have not been considered for the reasons set forth on PTO form 303."

Again on page 6 in Section 6 of the Advisory Action, mailed on August 16, 1999, the Examiner stated:

> "Applicant argues that the Epstein Declaration addresses the instant rejection. The argument has been noted but has not been found persuasive because the Declaration has not been considered for the reasons set forth on PTO form 303.

The reason given in both Sections 3 and 6 of the Advisory Action for the Examiner not considering either of the two Declarations as set forth on PTO Form 303 of the Advisory

Action of August 16, 1999 in item 5 is that:

> "The affidavit on exhibit will not be considered because the applicant has not shown good and sufficient reasons why it was not earlier presented."

It is submitted that this reason is rendered moot by the filing of the subject Continued Prosecution Application (CPA) and that since the Declarations are timely filed in the CPA Application, it is necessary for the Examiner to consider each of the Declarations under 37 CFR § 1.132. in examining the CPA application. See MPEP 716.01:

> "*(B) Consideration of evidence*
>
> Evidence traversing rejections must be considered by the examiner whenever present. All entered affidavits, declarations, and other evidence traversing rejections are acknowledged and commented upon by the examiner in the next succeeding action. The extent of the commentary depends on the action taken by the examiner."

B. The following are submissions, comments, and arguments in response to the numbered Sections of the Official Advisory Action, mailed August 16, 1999.

Action, Section 1(a'), page 3

> "...general methods of indoxyl chemistry, preparation of precipitable material and methods of radio labeling have been taught but the specification does not provide guidance on or exemplification of making or using the broadly claimed agents that would be therapeutic when administered *in vivo* and Applicant admits on the record that the therapeutic agent is only therapeutic after conversion. Without working examples that demonstrate that the conversion takes place *in vivo* which would provide guidance to one skilled in the art, given the issues raised in Paper No. 10, one of skill in the art could not predict that the therapeutic agent taught could be used with a reasonable expectation of success."

Response:

The Examiner agrees with the applicant that "the general methods of indoxyl

chemistry, preparation of precipitable material and methods of radiolabeling have been taught." In short, the Examiner agrees that adequate exemplification exists in the specification for making the therapeutic agent claimed in the present invention.

Further support for the adequacy of the disclosure and enablement can be found on pages 2-4 of the Declaration of Professor Rapoport. Professor Rapoport argues that the description of the present invention in the specification and the references cited in the specification enable one familiar with organic chemistry and of skill in the art to make the various soluble precipitable materials, including the therapeutic agent, disclosed in the '590 application.

Applicant argues that use of the claimed therapeutic agent is adequately disclosed in the present invention to one of skill in the art who is familiar with the general field of cancer and with the extensively published literature on antibody dependent prodrug enzyme therapies (ADEPT). Applicant argues and is additionally supported on pages 2-6 of the Declaration of Professor Epstein, that the present invention builds on the field of ADEPT and that the specification enables one of skill in the art and familiar with the field of ADEPT to practice the present invention, including protocols and required dosages. Thus the method of the present invention calls for the introducing of a bispecific reagent with an enzyme moiety (analogous reagents and dosages as the first step of the ADEPT procedure) and the subsequent administering of the therapeutic agent which is a soluble precipitable material (the ADEPT approach calls for the administration of a soluble pro-drug).

As discussed in the specification and references cited on pages 9-10 thereof, ADEPT achieves the conversion of an inactive pro-drug into an active drug via the enzyme action of a bispecific reagent that has been previously bound to the surface of cancer cells, and "since the enzyme moiety is bound to the surface of the targeted cells, the conversion from pro-drug to the active drug takes place in the extra-cellular fluid" (page 9, line 10-12). The references cited by the applicant on pages 9-10 of the specification describe in detail that the site of conversion of the pro-drug into the active drug occurs around the enzyme moiety of the

bispecific reagent bound to the surface of the cancer cells. Further, the International Patent Application, Publication Number WO 91/09134, cited by the Examiner, also describes that the *in vivo* site of conversion of the pro-drug is well-known and occurs at the target cancer cells even though:

> "the pro-drug itself is present in blood and other organs and tissues in an inactive form; only in the vicinity of the target cancer tissue is the pro-drug decomposed and activated by the anti-human-cancer-protein-complex of the present invention, as bound to human cancer cells." (page 2, lines 16-20).

In summary, the well-studied and widely published field of ADEPT provides many *in vivo* examples that the *in vivo* enzymatic conversion of the therapeutic agent claimed in the present invention will similarly occur in the vicinity of the target cancer tissue to which the first bispecific reagent is bound and, therefore, enables one of skill in the art to practice the present invention with confidence and without undue experimentation.

Furthermore, in the present invention, the claims, e.g., claims 1 and 69 and the specification of the application (pages 20-23) teach that the precipitation of the therapeutic agent occurs via non-mammalian enzyme action, such as the action of penicillinase, lacatamses, and other non-mammalian enzymes.

One of skill in the art would understand that according to the method of the present invention, the only non-mammalian enzymes in the subject host capable of achieving the soluble to insoluble conversion of the therapeutic agent are those present on the first bispecific reagent which is bound to the non-endocytosing receptors on the first target cancer cells.

For this reason it is also known to one of skill in the art that the conversion of the therapeutic agent can only take place *in vivo* at the location of the bound bispecific reagent and thus it is further known to one of skill in the art that the therapeutic agent could be used according to the method of the present invention with a very high probability of success.

The Applicant again submits that the therapeutic agent is not therapeutic *per se*.

Rather, according to the specification and claims of the present invention, the therapeutic agent (formerly known as the first therapeutic agent) has not been formed to have a therapeutic effect. As disclosed and referenced in the claims and specification, the therapeutic agent is administered in order to achieve the conversion of a large amount of soluble precipitable material into an insoluble first extracellular precipitate which is retained in the extracellular fluid adjacent to the first bispecific reagent which itself is bound to the target cancer cells. According to the method of the invention, the first extracellular precipitate is later used to achieve the conversion and retention of the additional therapeutic agent, which is a soluble radioactive toxic agent, into a new first extracellular precipitate for an extended period of time sufficient to kill non-selectively all cells adjacent to the first extra-cellular precipitate; however, according to the specification (page 23) and the claims (claim 1, 69, 83) the therapeutic agent "can also be radio-labeled to be trace-labeled or to be radioactive-therapeutic" (page 23). As disclosed in the specification (pages 7, 10-11) and as us common knowledge in the field, the therapeutic effectiveness of any radioactive material is a function of the number of radio isotope atoms present and the length of time that the radio-isotope atoms are retained.

Action, Section 1(b'), page 3

> "...applicant is arguing limitations not present in the claims as currently constituted as immobilization of a radioisotope is not claimed,".

Response:

Immobilization of the extra-cellular precipitate is set forth by the Applicant in the specification (page 19-20, 24, 26-27, 33-36) and in the claims of the present invention (claims 1, 69). Specifically the claims recite that:

> "...the extra-cellular precipitate remaining in the extra-cellular fluid adjacent to the bispecific reagent for a period of time."

According to the specification of the invention, one of skill in the art would recognize that, if the therapeutic agent was radio-labeled (as set forth in claim 83), the result would be that:

> "the extra-cellular precipitate remaining in the extra-cellular fluid adjacent to the bispecific reagent for a period of time."

This would constitute the immobilization of radioisotope atoms in the form of the radio-labeled extra-cellular precipitate.

Action, Section 1(c'), page 3

> "...Applicant is claiming a therapeutic agent, not a method for conversion of a prodrug to a therapeutic agent. Applicant admits on the record that the claimed therapeutic agent is not therapeutic *per se*,".

Response:

See response to Action, Section 1(a'), page 3 above; response to Action, Section 1(b'), page 3 above; and response to Action, Section 4, page 5 below.

Action, Section 1(d'), page 3

> "...applicant is arguing limitations not recited in the claims as presently constituted as the claims are not drawn to immobilized radioisotope atoms,".

Response:

See response to Action, Section 1(a'), page 3, above; Action, response to Section 1(b'), page 3, above; and response to Section 4, page 5, below.

Action, Section 1(e'), pages 3-4

> "...it is clear that the limitation that the therapeutic agent is not a protein is not recited in the claims as presently constituted and further, other than claim 83, none of the claims are drawn to radio-labeled soluble precipitable material and none of the claims are drawn to immobilized reagents.

Without working examples, in view of the issues raised in Paper No. 10, one of skill in the art could not predict that the only location where the therapeutic agent will be immobilized will be at the site of the bispecific reagent,..."

Response:

See response to Action, Section 1(a'), page 3, above; response to Action, Section 1(b'), page 3 above; and response to Action, Section 4, page 5, below.

Action, Section 1(f'), page 4

"...the issue raised here was not that the specification does not describe protein and peptides as candidates for the soluble precipitable material but that Applicant's response was confusing because Applicant stated on the record that the specification does not describe proteins and peptides as candidates for the soluble precipitable material,..."

Response:

In claim 69 of the application, the Applicant claims the composition of the therapeutic agent "of at least one of peptides..."

Action, Section 1(g'), page 4

'...Applicant was invited to submit objective evidence to resolve this issue, no objective evidence has been submitted but Applicant has admitted on the record that "ultimately, the insoluble precipitate will be removed by convection and phagocytosis but such removal from tumor tissue will be slower than for normal tissues.'

Response:

Applicant argues that the specification of the application contains descriptions and objective evidence which supports the Applicant's claim that:

"ultimately, the insoluble precipitate will be removed by convection and phagocytosis but such removal from tumor tissue will be slower than for normal tissues."

For example, as described in the present invention, the insoluble precipitate is not removed from the area by phagocytic activity because macrophage and phagocytic activity in the tumor is reduced (see references in specification pages 35-36). In addition, in the present invention, the insoluble precipitate is not removed from the area by convective flow because tumors lack effective lymphatic drainage (see references in specification pages 35-36). Numerous publications document and confirm the restricted movement of particles and macro-molecules in tumors compared to normal tissues. See for example the work of Clauss and Jain (1990) cited on page 30 of the specification.

Applicant further argues that objective support for the above claims is found on page 7 of the May 24, 1999 Declaration of Professor Alan Epstein, M.D., Ph.D.

Action, Section 3, page 5

> "If the amendment to the claims were to be entered, claims 69-83 would remain rejected under 35 USC 112, first paragraph essentially for the reasons disclosed in Paper No. 10, Section 5(d) 11 and Paper No.15, (sic) 18, Section 8, page 7. Applicant argues that Declarations of Professor Rapoport and Dr. Epstein are drawn to the issue raised. The argument has been noted but not found persuasive because the Declarations have not been considered for the reasons set forth on PTO form 303."

(Action, Paper No. 10, Section 5(d), page 11 - Action mailed February 25, 1998, redated March 18, 1998)

> "The specification gives no guidance on or exemplification, either *in vivo* or *in vivo*, of making, using a therapeutic agent in which a cell-impermeant chemical is attached to the first therapeutic agent, the cell impermeant chemical causing the first therapeutic agent to be cell impermeant wherein the cell impermeant chemical is selected from the group including materials having a molecular weight greater than 1000 daltons (claim 72). Clearly, as broadly written, the claim reads on any chemical that is greater than 1000 daltons and just as clearly, the specification has not taught how to make or use any therapeutic reagent conjugated to any chemical of unlimited molecular weight. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from

the disclosure of to make/use a therapeutic agent in which a cell-impermeant chemical is selected from the group including materials having a molecular weight greater than 1000 daltons that would function as claimed. Therefore, undue experimentation would be required to enable the claims."

(Action, Paper No. 18, Section 8, page 7 - Action mailed November 25, 1998)

"Applicant argues that making the soluble precipitable material into a cell impermeable molecule is disclosed on pages 19, 22 and 29-30. The recitation of materials having a molecular weight of greater than 1000 Daltons defines a large molecule and thereby a cell impermeant chemical. The argument has been noted, but has not been found persuasive. Further, the issue raised here was not the definition of a large molecule that is cell impermeant but rather the issue raised was how to use a large molecule, as broadly claimed, that will function as claimed."

Response:

In the response to the Official Actions, of Paper No. 19 and Paper Nos. 10 and 18, Applicant argues that the method of making a soluble precipitable material into a cell impermeant molecule is disclosed in the specification on pages 19, 22, and 29-30. On page 19 of the specification, Applicant describes the need for the therapeutic agent to be cell impermeant and further describes how cell impermeant can be readily achieved by attaching to the therapeutic agent "one of a number of cell impermeant molecules at least including peptides or polymers having a molecular size greater than 1,000 daltons and anionic chemicals including thiols."

As disclosed on page 4 in the Declaration of Professor Emer. Henry Rapoport, dated May 24, 1999 and submitted in support of Applicant's Amendment, filed on May 25, 1999, the practice of attaching molecules, such as polymers or peptides with a molecular weight of greater than 1,000 daltons and/or making materials anionic, is frequently practiced. Further the Declaration of Professor Emer. Henry Rapoport argues that sufficient information about the chemistry of the soluble precipitable material is disclosed in the specification of the application to enable one of skill in the art to attach such molecules to the soluble precipitable material.

Finally, as disclosed on pages 7 and 8 in the Declaration of Professor Alan Epstein, dated May 24, 1999 and submitted in support of the Applicant's Amendment, filed on May 25, 1999, it is well known to one of skill in the art that:

> "the attachment of large and/or anionic molecules to a product will make the resultant product cell impermeant."

Further the Declaration of Professor Alan Epstein describes how the attachment of such molecules to achieve cell impermeant of various products is widely published and frequently used. Thus, one skilled in the art would readily expect the soluble precipitable material disclosed in the present invention to become cell impermeant and function as described in the specifications and claims if a polymer or peptide with a molecular size greater than 1,000 daltons were attached.

Action, Section 4, page 5

> "If the amendments to the claims were to be entered, claims 69-82 would remain rejected under 35 USC 112, second paragraph essentially for the reasons disclosed in Paper No.10, Section 6(e) and Paper No. 15 (sic) 18, Section 9, page 7.
>
> Applicant argues that the therapeutic agent is radioactive and therefore must cause some cell damage. The arguments have been noted but have not been found persuasive because applicant is arguing limitations not recited in the claims as presently constituted."

(Action, Paper No. 10, Section 6(e), page 12 - Action mailed February 25, 1998, redated March 18, 1998)

> "Claims 69-83 are indefinite because it is not clear whether the first therapeutic agent is therapeutic before or after conversion to the insoluble and non-digestible precipitate or whether the therapeutic agent is neutralized or destroyed by the conversion process."

(Action, Paper No. 18, Section 9, page 7 - Action mailed November 25, 1998)

> "Applicant argues that, as drawn to rejection 6(e) that the therapeutic agent is radio-labeled. The argument has been noted but has not been found persuasive as drawn to claims 69-82 because radiolabeling is only claimed in claim 83 which is dependent upon claim 69."

Response:

According to the preferred method of the present invention, as described on pages 18, 19, and 24 of the specification and in claims 1-68, the therapeutic agent (originally referred to as the first therapeutic agent) is not therapeutic *per se*. Rather, the present patent application discloses a novel multi-step method for the treatment of cancer and further discloses the novel compositions required for that multi-step method for treatment. According to the method of the present invention, after the introducing of the first bispecific reagent, the therapeutic agent, which is a soluble precipitate material, is administered to the living host. When the therapeutic agent comes into contact with the enzyme moiety of the first bispecific reagent which is bound to the cancer cells, the therapeutic agent is converted into the first extracellular precipitate. The method of the present invention further describes continuing the introducing of the therapeutic agent "to increase the amount of first extracellular precipitate forming in the extra-cellular fluid." As disclosed in the "Description of the Preferred Embodiments" section of the specification and in the claims, the accumulation of the first extracellular precipitate does not produce a therapeutic effect. Rather, the accumulation of the first extracellular precipitate serves as a launching pad from which therapeutic regions of supra-lethal radiation, called Hot-Spots, are generated. (As described in the specification, the Hot-Spots are generated via conversion of the additional therapeutic agent, which is a radioactive toxic agent, into a new form which remains adjacent to the first extra-cellular precipitate. The additional therapeutic agent is converted into the new form via the action of the non-mammalian enzyme moiety at the second bispecific reagent which is bound to the first extra-cellular precipitate.)

According to the specification (page 23, Figs. 15-17) the "first therapeutic agent can be radio-labeled to be trace-labeled or to be radioactive therapeutic." If the therapeutic agent is prepared to be radioactive therapeutic, then, as described in the Applicant's Amendment, dated September 18, 1998 on page 15, section 21, the therapeutic agent is "only therapeutic after it has been converted into an insoluble material." The therapeutic potential of any radioactive material is a function of the amount of radioactivity (number of isotope atoms) present and the length of time the radioactivity remains at any given location. In the present invention, if the therapeutic agent is prepared (according to claim 83) with a radio-label which is to be radioactive therapeutic, the therapeutic agent would emit a very small amount of its energy during the short time that it remained in circulation; however, when the radioactive soluble precipitable material is converted into the first extracellular precipitate by the enzyme moiety of the first bispecific reagent, the radio-isotope atoms would remain immobilized and would be retained at the sight of conversion. The long retention time of the now-converted radioactive therapeutic agent would produce a Hot-Spot that would kill non-selectively those cells in the immediate microregion.

Action, Section 5, page 5

> 'If the amendment to the claims were to be entered, claim 79 would remain rejected under 35 USC 112, second paragraph essentially for the reasons disclosed in Paper No. 10, Section 6(s) and Paper No. 18, Section 9, page 8.
>
> Applicant argues claim 79 has been amended to provide a better definition of the invention. The argument has been noted but not been found persuasive because the amendment did not include the deletion of the indefinite term "derivatives."'

Response:

Claim 79 has been amended.

Action, Section 6, page 6

"If the amendment to the claims were to be entered, claims 69-82 would remain rejected under 35 USC 102 essentially for the reasons disclosed in Paper No. 10, Section 8 and Paper No. 15, Section 10, pages 8-9.

Applicant argues that the Epstein Declaration addresses the instant rejection. The argument has been noted but has not been found persuasive because the Declaration has not been considered for the reasons set forth on PTO form 303."

(Action, Paper No. 10, Section 8, pages 17-18 -Action mailed February 25, 1998, redated March 18, 1998)

"The reference (International Publication No. WO91/09134) does not specifically teach that the therapeutic reagents are adapted to be converted into insoluble and non-digestible precipitates. However, the claimed therapeutic agents appears to be the same as the prior art therapeutic agents, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences."

(Action, Paper No. 18, Section 10, pages 8-9, - Action mailed November 25, 1998)

"Claims 69-82 remain rejected under 35 USC 102(b) for the reasons previously set forth in Paper No. 10, Section 8 pages 16-18.

Applicant argues that present invention comprises the conversion of a soluble precipitable material into an insoluble and non-digestible precipitate by the enzyme moiety of the bispecific reagent which remains adjacent to the bispecific reagent for an extended period of time thus the precipitate does not enter the body system fluids and that conversion of a soluble precipitable material into an insoluble and non-digestible precipitate is not shown or suggested by WO91/09134 which recites only soluble, digestible, and active drugs that do not have epitopes and do not have neo-epitopes which are not radioactive and are not use to bind any other bispecific reagents. The argument has been

noted but has not been found persuasive because of the broadly recited pro-drugs disclosed in WO91/09134. Applicant is invited to submit objective evidence to establish that the product of the prior art does not posses the same material, structural and functional characteristics of the claimed product, particularly as drawn to the anti-cancer drugs recited on page 9, line 14 through page 11."

Response:

Applicant submits that the claimed invention is patentable over the prior art described in International Patent Application, Publication No,. WO91/09134, because the method and compositions disclosed in the '590 application are materially different and distinct from the method and compositions described in the above referenced International Patent. Objective evidence has been submitted in the form of a Declaration by Professor Alan Epstein, dated May 24, 1999.

As discussed in the Applicant's response dated September 18, 1998 (pages 21-22), in Applicant's response dated May 25, 1999 (page 22), and in the Declaration of Professor Alan Epstein, dated May 24, 1999 (pages 8-9), the first step of the method of the present invention is the same as the first step of the method described in International Patent Application, Publication No. WO91/09134 -- namely the administration of a bispecific reagent with two moieties, one moiety which binds to target cancer cells and, the other moiety containing a non-mammalian enzyme. This is the only similarity between the present invention and the prior art.

The final step of the method of the prior art disclosed in WO91/09134 is for the administration of "an inactive anticancer pro-drug" (page 2, lines 10-11). According to the method of the invention disclosed in the International Patent Application, the pro-drug is converted into an active drug by the enzyme moiety of the previously bound bispecific reagent with the drugs' "cytotoxic effect being exhibited regardless of the diversity of cancer cells."

The method of the invention disclosed in the subject application calls for the

administration of a therapeutic agent which is a soluble precipitable material which "can be radio-labeled to be trace-labeled or to be radioactive therapeutic" (specifications, page 23). The soluble therapeutic agent is converted by the enzymatic moiety into an insoluble precipitate which remains *in situ* adjacent to the bispecific reagent. If the soluble therapeutic reagent has been prepared with a radio-label, then the insoluble precipitate will also have the radio-label and because the insoluble precipitate remains in the tumor tissue extracellular fluid, the isotope atoms will exhibit their therapeutic effect and will produce a microregion of supra-lethal radiation around the precipitate which kills non-selectively those cells in the immediate microregion.

Further, the method of the present invention calls for the administration of a second bispecific reagent with two moieties. One moiety is a targeting agent for one of the epitopes on the precipitate formed from the therapeutic agent, the second moiety is a non-mammalian enzyme. The method disclosed in the prior art does not set forth the administration of any second bispecific reagent, let alone a second bispecific reagent which binds to one of the epitopes on the precipitate formed from a soluble precipitable material.

Further the method of the present invention calls for the administration of an additional therapeutic reagent, a soluble radioactive toxic material, which is converted by the non-mammalian enzyme moiety of the second bispecific reagent into a new form which remains in the tumor tissue for a period of time sufficient that the retained new form generates a region of sura-lethal radiation that kills non-selectively cancer cells in the immediate microregion of the new form. The method disclosed in the prior art does not set forth the administration of an additional therapeutic agent which is radioactive toxic and which is converted into a new form.

In addition, as detailed in the Applicant's response Paper No. 17, dated September 18, 1998 (pages 21-22), Applicant's response, dated May 25, 1999 (page 22), and in the Declaration of Professor Alan Epstein, dated May 24, 1999 (pages 8-9), the composition of the agents disclosed in the present invention are not disclosed in the prior art and are clearly

patentable over the prior art. In particular, the therapeutic agent and the additional therapeutic agent disclosed in the present invention are novel and are not shown or suggested in the International Patent Application. Thus the International Patent Application, Publication No. WO91/09134, discloses soluble pro-drugs which are converted into soluble active drugs. It does not disclose radio-isotopes and it does not disclose agents which are converted from being soluble to being insoluble. The therapeutic agent and the additional therapeutic agent claimed in the present invention are distinct from the pro-drugs described in International Patent Application, Publication No. WO91/09134, on page 10, lines 14-30, which exhibit "pharmacological activities." Pharmacological activities are to be exhibited by soluble drugs -- i.e. the term pharmacological activities describes the action of drugs on cells or tissues. Radiation is not a pharmacological action.

In summary, the International Patent Application is limited to the use of cytotoxic drugs which remain soluble and thus does not disclose agents or compositions which are radioactive and which can be converted into insoluble precipitates by enzyme action in accordance with the invention.

C. THE EXAMINER'S REJECTIONS IN SECTION 1 ON PAGES 3 AND 4 OF THE OFFICIAL ADVISORY ACTION ARE SIMPLY BASED UPON FACTS WITHIN THE PERSONAL KNOWLEDGE OF THE EXAMINER

The Examiner's Rejections in Section 1 on pages 3 and 4 of the Official Advisory Action, identified as (a') - (g'), directed to the Applicant's argument identified as (a) - (g), inclusive, in Section 1, pages 2 and 3 of the Action, are rejections based simply upon facts within the personal knowledge of the Examiner, not upon documentary proof in support of the Examiner's position.

The Applicant in accordance with MPEP § 2144.03 respectfully calls for an affidavit of the Examiner in support of the facts within the personal knowledge of the Examiner relied upon in Section 1 of the Action in rejecting the Applicants arguments identified by the Examiner as (a) - (g), inclusive.

The Applicant reserves the right to subject such an affidavit by the Examiner to contradiction or explanation by affidavits of the Applicant and other persons. (See 37 CFR § 1.104 (d)(2).)

D. THE REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH, IN SECTIONS 2 AND 3 OF THE OFFICIAL ADVISORY ACTION, BASED UPON THE PERSONAL KNOWLEDGE OF THE EXAMINER, ARE REFUTED BY THE DECLARATIONS OF PROFESSOR EMER. HENRY RAPOPORT, Ph. D. AND PROFESSOR ALAN L. EPSTEIN, M.D., Ph. D. WHICH ADMITTEDLY "...HAD NOT BEEN CONSIDERED..." BY THE EXAMINER

It's submitted that the Declarations submitted herein bear out that the enablement requirement of 35 U.S.C. § 112, first paragraph, has been met by the specification and original claims of the subject application.

As set forth in MPEP § 2164:

> "The enablement requirement refers to the requirement of 35 U.S.C. § 112, first paragraph that the specification describe how to make and how to use the invention. The invention that one skilled in the art must be enabled to make and use is that defined by the claim(s) of the particular application or patent. The purpose of the requirement that the specification describe the invention in such terms that one skilled in the art can make and use the claimed invention is to ensure that the invention is communicated to the interested public in a meaningful way.
>
> The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. Detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention. *In re Wands, 858 F.2d at 737, 8 USPQ 2d at 1404 (Fed. Cir. 1988) See also United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ 2d 1217, 1223 (Fed. Cir.1988).*"

As further set forth in MPEP § 2164:

> "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." A patent need not teach,

and preferably omits, what is well known in the art. *In re Buchner,* 929F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)."

E. MATTER AND INFORMATION IN THE ORIGINAL CLAIMS DEFEATS AN ALLEGATION OF "NEW MATTER" SINCE THE ORIGINAL CLAIMS ARE PART OF THE DISCLOSURE

The original claims are a part of the disclosure of an application, *In re Meyers* (CCPA 1969) 410 F2d 420, 161 USPQ 668, and the latter can be amended to conform with the former. Ex parte Wilson et al (POBA 1957) 116 USPQ 595.

In MPEP § 608.1(1) - "Original Claims" recites:

> "In establishing a disclosure, applicant may rely not only on the description and drawings as filed but also on the original claims if their content justifies it. Where subject matter not shown in the drawing or described in the description is claimed in the case as filed, and such original claim itself constitutes a clear disclosure of this subject matter, then the claim should be treated on its merits, and requirement made to amend the drawings and description to show the subject matter.

In MPEP § 608.4 - "New Matter," it is recited:

> "In establishing a disclosure, applicant may not only rely on the specification and drawing as filed but also on the original claims if their content justifies it."

In MPEP § 706.03.(o) - "New Matter," it is recited:

> "If subject matter capable of illustration is originally claimed and is not shown in the drawing, the claim is not rejected but applicant is is required to add it to the drawing."

In MPEP § 2163.06, it is recited:

> "Stated another way, information contained in any one of the specification, claims, or drawings of the application, as filed may be added to any other part of the application without introducing new matter."

In MPEP § 2163.06, "III," it is recited:

"The claims as filed in the original specification are part of the disclosure and therefore, if an application as originally filed contains a claim disclosing material not disclosed in the remainder of the specification, the applicant may amend the specification to include the claimed subject matter. *In re Benno*, § 768 1340, 226 USPQ 683 (Fed Cir. 1985)."

F. THE ADVISORY ACTION (PAPER NO. 19), MAILED AUGUST 16, 1999 ALLEGES, IN BOX 1. b., c., AND d., THAT THE PROPOSED AMENDMENT OF MAY 25, 1999 RAISED NEW ISSUES THAT WOULD REQUIRE FURTHER CONSIDERATION AND/OR SEARCH AND THAT THEY WOULD RAISE THE ISSUE OF "NEW MATTER"

In the Advisory Action under the NOTE of Box 1., it is recited that the proposed amendment:

'Raise the issue of reinstatement of § 112, 2nd (sic) proposed in Paper # 10, section 6 (k). Amendment of claim 71 to recite "molecule" broadens the scope and requires additional search'

In response it is submitted that in the first full paragraph on page 27 of the specification, it is recited:

"For these reasons it is of significant advantage for the additional therapeutic agent to be cell impermeant by being a molecule larger than 1,000 daltons and/or being anionic. Alternatively the additional therapeutic agent can be made cell impermeant by attaching one of a number of cell impermeant molecules at least including peptides or polymers having a molecular size greater than 1,000 daltons and anionic chemicals including thiols."

Further in the NOTE of Box 1. of the Advisory Action, it is recited:

'In claim 77 the phrase "to move by diffusion or convective flow" is not found in amended claim 77 in paper # 14 & is not shown as an amendment in paper # 17 but would require addn'l search and consideration as new matter as would claims 78-80 for the same reasons, further these claims are drawn to new matter, not suggested in the spec or claims as originally filed.'

Claims 77-80 as amended recite:

"...to reduce the ability of the indoxyl compounds and the extra-cellular precipitate to move by at least one of diffusion in convective flow

in the extra-cellular fluid."

It is submitted in response that the diffusion and convective flow in the extra-cellular fluid are clearly set forth in the specification, beginning in the bottom paragraph on page 29 and extending into page 30. Thus, it is recited:

> "A controlled diffusion away from the second enzyme moiety would have the advantage of distributing the radioactive toxic second precipitate more evenly throughout the tissue, thus increasing the size of the Hot-Spots and reducing the problem of tumor heterogeneity. On the other hand, if the diffusion away from the second enzyme moiety was extreme, it would allow the soluble indoxyl molecules to diffuse into the blood or lymphatic capillaries where it would dimerize, precipitate, and deliver radioactive precipitates to normal tissues and reduce the radiation dosage of the tumor. In order to obtain the advantage of control diffusion, and to circumvent the problem of the indoxyl diffusing into the blood, various modifications can be made to the indoxyl-lactam so that the rate of diffusion of indoxyl into blood capillaries is greatly reduced."

Again the NOTE of Box 1. of the Advisory Action recites:

> "...further these claims are drawn to new matter not supported in the spec or claims as originally filed..."

As set forth above, there is no question of "new matter" since the original specification clearly recited the moving of the indoxyl compounds and the extra-cellular precipitate in the extra-cellular fluid including diffusion thereof.

The Advisory Action under Box 3. goes on to say:

> "Applicant's response has overcome the following rejection(s): If the amendment to the claims were to be entered, rejection of Claim 69 under 35 USC 112 para would be withdrawn as drawn to rejection in paper # 10, Sections 6(f), 6(I), 6(L), & objection to Claim 69 would be withdrawn as would be the rejection of claim 69-83 under 35 USC 112, first paragraph in Paper # 15, Section 11, pages 9-10."

In view of this recitation in the Advisory Action, it is submitted that the amendments to the claims herein should be entered.

PUBLICATION EXHIBITS

Attached to the Amendment filed on May 25, 1999 were Exhibits A-J which are copies of papers in technical publications which bear out the state of the art of the background of the claimed subject matter of the invention of the application and thereby set forth the understanding of one skilled in the art relevant to the claimed invention at the time of the filing of the above-identified application.

A. References to ADEPT, Pages 1 and 2

B. Lymphatic drainage from the extracellular fluid of tumor tissue is impaired (leading to accumulation of macromolecules in this location), page 3

C. Macrophages are inhibited in tumor, page 4

D. Construction and Characterization of a Fusion Protein of Single Chain Anti-CD20 Antibody and Human β-Glucuronidase for Antibody-Directed Enzyme Prodrug Therapy. Blood, Vol. 92, No 1,(July 1), 1998: pp 184-190

E. Toward Antibody-directed Enzyme Prodrug Therapy with the T268G Mutant of Human Carboxypeptidase And Novel *in Vivo* Stable Prodrugs of Methotrexate. The Journal of Biological Chemistry, Vol. 272, No 25, June 20, 1997 pp 15804-15816

F. Use of conjugates of bovine serum albumin with poly(alkylene oxide)s For solubilization of riboflavin ester Biotechnol, Appl. Biochem. 17, 337-348 [1993]

G. The bioactivation of CB 1954 and its use as a prodrug in antibody-Directed enzyme prodrug therapy (ADEPT) Cancer and Metastasis Review 12: 195-212, 1993

H. Construction, Expression, and Activities of L49-sFv-β-Lactamase, Single-Chain Antibody Fusion Protein for Anticancer Prodrug Activation Bioconjugate Chem. 1997, 8, 510-519

I. Preparation and Characterization of a β-Lactamase-Fab' Cpmkigate for

the Site-Speciic Activation of Oncolytic Agent Bioconjugate Chem. 1992, 3, 42-48

J. Enhancement of the *in Vivo* Activities of Phosphorylated Mitomyin C and Etoposide Derivatives by Monoclonal Antibody-Alkaline Phosphatase Conjugates [Cancer Research 49, 5789-5792, November 1, 1989]

Exhibit A-E are particularly relevant to the Declaration of Alan L. Epstein, M.D., Ph.D., enclosed herewith.

Exhibit F is particularly relevant to the Declaration of Professor Emer. Henry Rapoport enclosed herewith.

Exhibits G-J are particularly relevant to the prodrug therapy ADEPT referred to in the specification of the above-identified application.

SUMMARY

It is submitted that the formal objections to claims 69-83 have been overcome by the amendments to the claims herein.

It is further submitted that claims 69-83 have been patentably distinguished over the reference (International Application Number WO 91/09134) which does not show, teach, or suggest that the therapeutic reagents are adapted to be converted into insoluble non-digestible precipitates as set forth in claims 69-83.

Therefore, it is submitted that claims 69-83 should now be found to be in condition for allowance.

Favorable action is solicited.

Respectfully submitted,

John Q. McQuillan

Dated: November 16, 1999

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